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Undergraduate Medical Research at the University of Toronto

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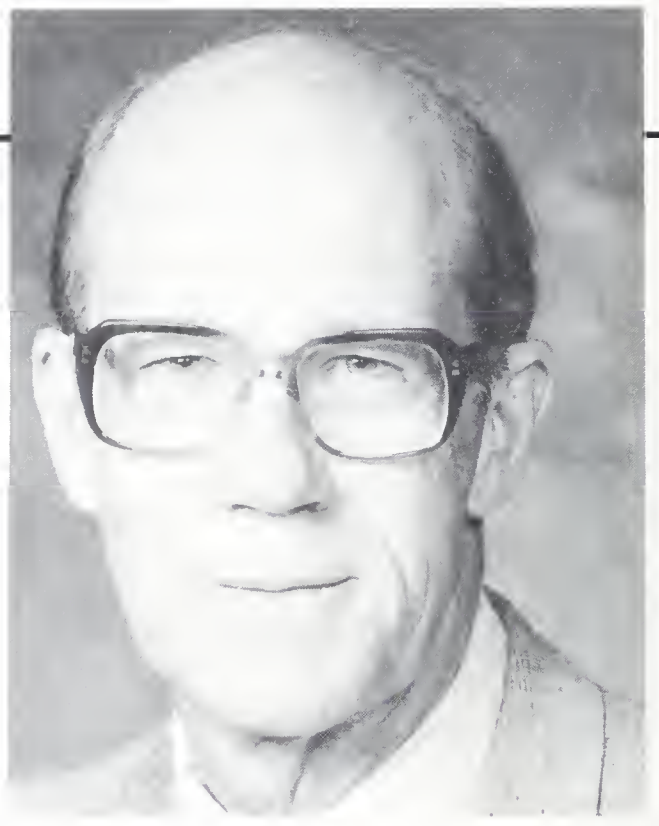
Vol. LXVII Supplement 2

Undergraduate Medical Research at the University of Toronto

John H. Dirks, M.D.
Dean, Faculty of Medicine



Ross Fleming
Associate Dean, Undergraduate Medical Education

Undergraduate Medical Student Research Day

A special event in the Undergraduate Medical School Program at the University of Toronto is the Student Research Day. This is a Faculty that has an international reputation in research and scholarship. It is singularly important that medical students be dedicated to developing new knowledge through their own research work. This year's display of posters indicates the high level of excellence and commitment that students have to research in this Faculty. I feel a great sense of pride in viewing these accomplishments and I congratulate all of you for it. I foresee that many of you will indeed push on to have illustrious careers in academic medicine. I look forward, in the next decades, to hearing and learning of your contributions to research and understanding of health and disease. The advancement of clinical medicine in the future will rest in your capable hands. You have made an excellent start.

You are entering the practice of medicine at a wonderful time, as virtually every day there are new scientific and clinical developments. It is great to have you as a part of the important endeavour of medicine. I know that you have found it, and will continue to find it, satisfying and fulfilling. Congratulations on your presentations.

John H. Dirks, M.D.
Dean
Faculty of Medicine

Summer Scholarship Program

The Faculty of Medicine is fortunate to offer a number of scholarships to first and second year medical students who undertake research projects during the summer.

This year approximately 90 such scholarships are available, each in the amount of approximately $3000. Scholarships have been provided by a number of private donors and agencies. Amongst these, the Faculty Scholarship Trust Fund provides 25 scholarships, our Medical Alumni Association provides 15, and the Medical Research Council of Canada provides 38. Other scholarships are provided by the Heart and Stroke Foundation of Ontario (3), CIBA Geigy (1), Leukemia Research Foundation (1), Lela Parlow Cancer Research Fellowship (1), R.J. Wilson Award (1), Nu Sigma Nu Fraternity (2), Women's Breast Cancer Foundation (2), and the Pharmaceutical Manufacturers Association of Canada (3). Some scholarships are designated for specific areas of research, and others are more general.

All Year 1 and Year 2 students who are enrolled in our undergraduate medical program are eligible to apply for a summer scholarship. Over 400 opportunities that qualify for summer scholarships are listed in the Summer Scholarship Catalogue, and amongst these are many outstanding research experiences. Included in the catalogue is a list of Faculty members willing to act as supervisors. Students may also apply for scholarships to fund opportunities not listed in the catalogue.

Applications providing a detailed description of the proposed project and approved by the supervisor must be received in the Undergraduate Medical Education Office by mid-February. All applications are reviewed on the basis of the specific details of the proposal received, the commitment of the student and the supervisor to the project, and the relevance to the student's education and career goals. Scholarships are awarded on a competitive basis.

The program, together with the elective time available during the academic year, provides an excellent opportunity for students to develop or continue their research interests as well as to explore future career interests in basic or clinical research.

I wish you the very best during your school year and in your summer endeavours.

Ross Fleming
Associate Dean
Undergraduate Medical Education

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Student Research Day

The 1989 Student Research Day was a success with 53 posters. According to the judges, the quality of research displayed and its presentation exceeded previous years. I would like to thank all of the students who participated and the panel of judges (Drs. Bayliss, Csima, Murray, Salerno, Whiteside and Wiley). Also, I am indebted to Dr. Ruth Kurdyak and the Alumni Association who provided funds for 3 prize winners (Martin Breton, Barry Sullivan and Patrick Lo) to travel to and present their work at the National Research Forum in Galveston, Texas in April.

The 1989 Research Day ended my responsibility for organization. With this change, it seems like an appropriate time to take stock of achievements and look for new and innovative ways to develop student interest in research.

It is evident that the Student Research Day has succeeded because of the willingness of students to take part and because a small number of staff gave their time and effort. However, after four years, we still attract only a small proportion of students and attendance by staff has not been as high as I think it should be. Moreover, we look to Galveston as the major North American event for students to present their work.

Obviously better publicity about the event is necessary to increase attendance. We also need a solid funding base to support some students in developing their poster boards. As you know, so far, we have operated on a zero budget and used room dividers as a means to hold posters. The time has arrived to consider establishing a Canadian student research forum open to students of Canadian medical schools. University of Toronto students presumably would host the first few of these forums and then move it to other Canadian medical schools on a rotating basis.

Finally, the place of students in the undergraduate curriculum is under review by a committee chaired by Dr. A. Angel (Institute of Medical Science). The newly formed Curriculum Renewal Task Force headed by Dr. K. Shumak, the designated Associate Dean, Undergraduate Medical Education, will also be considering the role of student research. Shelley Boyd, a Year II student and former participant in Student Research Day, is the student representative on the Task Force. Please write or contact Shelley and/or Dr. Angel to express your views on student research and its future.

Niall Byrne, PhD
Student Research Day Organizer

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EDITORIAL

The University of Toronto Medical Journal proudly presents this supplemental issue highlighting the cumulative student efforts behind the highly successful fourth annual Student Research Day, December 5th, 1989. The event itself is designed to provide a forum for students in the Faculties of Medicine and Arts as Applied to Medicine to present original research in poster form. The abstracts representing fifty-three contributions from the 1989 proceedings are gathered here.

One glance suffices to demonstrate the dedication and high level of commitment to each and every project. Each submission represents countless hours of work. As colleagues, it is important to acknowledge those amongst us who actively strive to further our knowledge in the areas of basic science and clinical medicine. Research Day and this publication function in this endeavour.

Efforts in the future will concentrate on heightening awareness of the event both in and around the University of Toronto, as well as providing a model for other universities to follow. The ultimate aspiration lies in the establishment of a (Canadian) national student research day.

With respect to this issue, we would like to thank all presenters for submitting an abstract for publication. In addition, Dr. Niall Byrne, his staff, and other Faculty members have been instrumental in the success of the 1989 Research Day/supplemental publication by donating freely of their time. Lastly, we would like to encourage all of you to peruse this Supplement, with a vision of your contribution to the future in mind.

Carol Geller
Nicola Richmond
Supplement Editors

HOUSING AND TRACKING MOVEMENT OF STREET YOUTH

D. Sit

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

This study investigated where street youth go during the day and where they stay at night. Two hundred street youth participated in the housing survey and 164 in the tracking survey. Seventy percent of those interviewed were male. The average age was 19-20 years old. Data showed that approximately 85 percent of street youth came from urban backgrounds: almost half from either metropolitan Toronto or its suburbs, and approximately one-quarter from southern Ontario. The remainder came from northern Ontario and the rest of Canada. The average stay 'on the street' was three to four years. The most popular cities for youth to stay (apart from Toronto) were Hamilton, Ottawa, Montreal, Vancouver, American cities, and the suburbs of these cities. The types of places that street youth stayed in were: their own 'homes' (3-4 months), with friends (2.5 months), with parents (3 months), group homes (2.5 months), hostels (1.5 months) and other places such as jail (2.5 months), on the street (2 months), rehabilitation programmes, squats, and so forth (2 months). With a city as large as Toronto, where the "regular, economically stable" population already find tremendous difficulty in affording a place to live, street youth are a low community priority with respect to the provision of affordable housing. Conclusions of this study were that housing has an impact on the mental and physical health of street youth. This impact is negative because of the instability of housing situations for street youth and the lack of sanitary living conditions for most of them. Street youth stay in places and go to places that put them at risk of becoming victims of violence. Health care professionals need to be aware of the life situations of their street youth patients in order to provide holistic and realistic health care.

FUNCTIONAL LIFESTYLE ANALYSIS OF STREET YOUTH

J. J.-H. Kim*

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

A large underground population and subculture estimated to be composed of 15,000 runaways and youth live on the streets of downtown Toronto. Although their numbers increase yearly, little is known about their lifestyle and how they survive on the street; areas which impact directly on their mental and physical health, their access to health care and their health needs. This study assessed the functional lifestyles of street youth in downtown Toronto during a 3-month period in order to evaluate their life skills and their means of survival. A questionnaire addressed areas such as street youth shelter, hygiene, nutrition, education, literacy, employment, and survival from crime. Preliminary results show that most street youth have completed a Grade 9 level education. Almost all were not engaged in any alternative form of schooling while on the street. Although most denied problems reading, many could not read the questionnaire form. Both hygiene and nutrition improved if the individual was staying in a formal shelter with access to bathing facilities and regular meals. Approximately sixty percent stated that they had been employed in the past year although most were not working at the time of the interview. A significant number was involved in at least three forms of survival crime which usually included mugging, shoplifting, and drug dealing. The conclusion of the study was that the lifestyle of street youth negatively influenced their physical and mental well-being.

STREET YOUTH AWARENESS OF THE HEALTH CARE SYSTEM

B. Ling* and R. Jetly

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

The prevalence of street youth in the downtown core of Toronto is estimated to be 15,000. By means of a health needs analysis survey, the authors assessed street youth awareness of the health care system. Street youth were surveyed at the Evergreen drop-in centre, Covenant House, and on the streets of downtown Toronto during the summer of 1989. Results showed that the majority of youth have an OHIP number and are aware of either a family doctor or a hospital which is available to them for health care. The findings suggest that the street youth have access to the health care system. However, it was also found that these services are not being used by the youth. They are aware of the services, but they do not use them unless their problem becomes acutely severe. The conclusion of the study was that strategies have to be developed to protect the health of the community and of street youth and that appropriate health care needs to be established for the street youth of Toronto.

ANALYSIS OF FAMILY BACKGROUND OF STREET YOUTH

K. Cheung*

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

The streets of downtown Toronto are inhabited by many homeless youth. Recent surveys indicate that 15,000 homeless youth live in the inner city. To date, minimal information is available on the specific needs, habits, and backgrounds of these youth. The purpose of this study was to gain an understanding of the types of family backgrounds from which a sample of street youth came. Two hundred and two youth participated in a health needs survey. Preliminary results indicate that a majority of the youth were raised by people other than their natural parents for at least some period of their childhood and adolescence. A significant number did not know their natural parents. Substance abuse in the home (natural parents or adoptive/foster parents) was prevalent. Ninety percent of the youth surveyed reported being subjected to physical, sexual, and/or emotional abuse in their homes and outside their homes. Results of this survey indicate that the street youth of downtown Toronto are a significant subpopulation which lacks the stability and security of family structure and support. This has an impact on their physical and emotional health and on the way they access and use health services. The conclusions of the study were that street youth are a special population which is disadvantaged in the health care system and that they need special consideration where health care is concerned.

HEALTH NEEDS OF STREET YOUTH: THE EVERGREEN PROJECT

K. Cheung, R. Jetly[a], J. Kim, B. Ling, A. Pearl, D. Satok, and D. Sit

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

Recent studies show that more than 15,000 young people live on the streets of Toronto without obvious links to family, employment, housing, or health care. This population has a high incidence of medical problems which are largely untreated. The study examined health needs of street youth using a 59-item survey to identify their family backgrounds, education, literacy, housing, employment, past medical history, present health status, family health (if known), sexual history, and use of mood-altering substances. It asked street youth how they would design a health care system to meet their needs. Results showed that street youth have major medical and social problems which are not being treated. These problems can have serious sequelae. Conclusions were: (1) ambulatory care for street youth has to adopt street-youth appropriate strategies in order to be effective; (2) some of the youth surveyed are likely to become the future 'skid row'; (3) a significant number of those surveyed would not survive long due to excessive drug and alcohol abuse, suicide (one committed suicide during the course of the study), and street violence; (4) there was a need to educate physicians and medical students about the health needs of this group.

HEALTH NEEDS ASSESSMENT OF TORONTO STREET YOUTH: PRIMARY MEDICAL ILLNESSES

A.J. Pearl[a]*

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A subculture of street youth in Toronto's downtown core has been identified and estimated to be 15,000 people. There is some evidence that these youth suffer numerous medical illnesses for which they may not receive adequate medical/health care. A survey consisting of 59 items was developed and used to interview youth (N=202) who presented over a three month period to a downtown drop-in centre or who were approached on city streets. Relevant data relating to mental illness, life skills, housing, and current health care concerns were collected. This study investigated the prevalence of subject-reported medical illnesses including primary eye and dental problems. Preliminary results show that approximately 70 percent of all street youth suffer repeated upper respiratory tract infections, with 73.8 percent reporting coughs and 66.7 percent reporting sore throats. Headache pain of a variable nature was experienced by 71.4 percent, while 45.2 percent reported symptomatology consistent with ear infection and 40.5 percent suffered bouts of diarrhea. Other medical conditions included sexually transmitted diseases, conjunctivitis, foot problems, and infected sores. Many of the females were pregnant or had been pregnant. Only 16.6 percent reported having seen a dentist within the preceding six months and 59.9 percent reported a need for eye care. The conclusion of the study was that street youth suffer many medical illnesses which may be related to their physical lifestyle, socioeconomic status, and psychiatric or educational background. Their poor physical health not only represents an acute treatable medical problem, but also serves as a marker for future chronic difficulties. The delivery of health care to this population needs to be adjusted and modified accordingly so that 'street wise' and ambulatory services are available.

THE MENTAL HEALTH OF STREET YOUTH

D. Sato[k]*

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Toronto, Ontario

A growing subculture of street youth has been identified in the downtown core of Toronto. According to recent studies, 15,000 homeless youths make up this population. The present study employed a questionnaire to examine the mental health status of street youth in Toronto. Risk factors for the development and continuation of poor mental health were also identified and examined. Two hundred and two surveys were completed over the three month study period and used to tabulate the results. Critical determinants of mental health were found to be: nurture insufficiency, physical illness, dissolution of the family unit, physical and sexual abuse, and both thoughts of and attempts at suicide. Results indicated that a majority of the youths were raised by people other than their natural parents during periods of their childhood and adolescence. A significant number did not even know their natural parents. A high incidence of family break-up was also reported. Parental substance abuse was indicated as a major cause of family discord by many of those surveyed. An alarming 90% incidence of physical and sexual abuse was shown. Physical illness was another common finding with a significant number of street youth reporting coughs, colds, flu, sexually transmitted diseases and foot problems. The street youth population was shown to be at a particularly high risk for suicide. Fifty-seven percent of those surveyed said they had thought about suicide. Forty percent admitted to having attempted suicide, with 47% of these reporting multiple attempts. Given the above results it was not surprising that when mental health was examined a large number reported feeling depressed either always or almost always. Anger was another highly indicated emotion, with 31% of those surveyed feeling angry either always or almost always. It was concluded that street youth are at a higher risk for developing and potentiating mental illness. This was due to their physical lifestyle, social and psychological backgrounds, and poor prospects for leaving the street. A need for mental health professionals to work with this highly underserviced population was also identified.

THE MEDICAL EFFECTS OF NUCLEAR WAR

N.S. Ming[o]*

Department of Behavioural Science, Division of Community Health, Faculty of Medicine, University of Toronto, Ontario

Physicians have long been interested in the medical consequences of nuclear war, not only for victims who would die shortly after an attack, but also for the potential survivors. The health records of the atomic bomb survivors of Hiroshima have been used in an effort to anticipate the medical effects of nuclear war. The consequences can be divided into blast injuries, damage caused by ionizing and ultraviolet B radiation, thermal burns, malnutrition, and psychological stress. Of the estimated 350,000 people exposed on August 6, 1945 in Hiroshima, there were 118,661 fatalities. Over 90% of the deaths occurred during the first two weeks after the explosion; most of these due to thermal or blast injuries. The ground surface temperature of the hypocentre is believed to have reached 3,000 to 4,000 degrees Celsius, causing thermal burns on the exposed skin of people within 3.5 km. The pressure directly below the explosion was estimated to be between 4.5 and 6.7 tons per square meter. Blast injury mortality rates ranged from 50 to 100% within 1 km of the hypocentre, depending on the degree of shielding. The radiation has been held responsible for the observed increased incidences of leukemia, multiple myeloma, and other cancers, as well as cataracts, chromosomal abnormalities, and fetal abnormalities in survivors. Many of the long term immunological effects have only recently been studied, and include decreases in functional T cell responsiveness. The work in the field suggests that the most potent medical effect of nuclear war is the synergy between the various insults, all of which depress the immune system and leave potential survivors vulnerable to opportunistic infections.

RETURN TO WORK IN CARDIAC PATIENTS: A PROSPECTIVE, LONGITUDINAL STUDY

W. G. Cavner*

School of Psychology, University of Ottawa, Ottawa, Ontario

A number of studies (Boulay et al, 1983; Schiller et al, 1976; Stanton et al, 1983) have suggested that it is possible to predict return to work for cardiac patients on the basis of several demographic, occupational, and social psychological variables. The Vocational Prognosis Form (VPF) has been developed as a short paper and pencil test that provides simple, feasible measures of variables that research has shown to be relevant to cardiac patients' return to work. The present study was designed to assess the predictive power of the variables contained in the VPF vis-a-vis whether the patients returned to work, the length of time taken by the patient to return to work and the ease with which the return was accomplished. Subjects were 189 cardiac in-patients at the University of Ottawa Heart Institute. Subjects were administered the VPF by telephone 14 to 21 days after discharge from the Heart Institute. Six and twelve months later the Vocational Follow Up Form (VFF) was administered to determine whether, how quickly, and how easily he or she returned to work. Hierarchical regression analysis was used to assess the incremental predictive power of the variables measured by the VPF. The most consistent predictors of RTW were found to be the patient's perception of his or her physician's attitudes towards their return to work, the patient's confidence in being able to return to their old job with their old employer, and the length of time that the patient was off work. The results provide encouraging support for the utility of the VPF for predicting return to work in cardiac patients.

RESPONSE OF METASTATIC BREAST CANCER TO SINGLE-AGENT ADRIAMYCIN GIVEN ON A WEEKLY SCHEDULE: RESULTS & ANALYSIS OF CRITERIA FOR RESPONSE

A.S. Pandey*, R. Buckman and K. Pritchard

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The anthracycline cytotoxic drug doxorubicin (Adriamycin [ADR]) is active in breast cancer (Ca breast) metastases resistant to hormone or standard multi-agent cytotoxic chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF). Given on a weekly schedule, ADR is well tolerated with little nausea and a low incidence of alopecia. A retrospective chart review was carried out to determine the response rate (RR) of metastatic Ca breast to weekly ADR and to analyze different methods of reporting responses as used by different investigators in the world literature. Seventy-three patients were identified by the clinic's patient registry as having received ADR for metastatic Ca breast. Of the 73, 38 had received ADR in combination with other drugs, and 35 had received weekly ADR only. Of these 35 patients, 4 were unassessable (less than four weeks of ADR therapy), 14 had objective evidence of progressive disease, 5 experienced subjective response (relief of pain, dyspnea, etc), 6 had stable disease and 6 had objective response by UICC criteria (3 partial responses, 3 complete). By the strictest criteria (UICC) the objective response rate to weekly ADR was 17%. If subjective responses had been included the RR would have been 31%, including stable disease it would have been 49%, and if the unassessable patients had been excluded it would have been 55%. The importance of specifying the criteria by which the RR is measured and the possible disparity of reports in the literature was discussed.

A CASE REPORT OF A MASKED REACTIVE DEPRESSION ASSOCIATED WITH BIZARRE SELF-DESTRUCTIVE BEHAVIOUR IN AN ELDERLY WOMAN

M.F. Pare, S. Zacks*, R.S.P. Kogucki, C. Chang and A.J. Braganza

St. Joseph's Health Centre and the Department of Art as Applied to Medicine, University of Toronto, Toronto, Ontario

Mrs. J. is a 75 year old Ukranian woman who was widowed three months prior to her presentation to the emergency room. She lives by herself in her own home in Toronto. Chief complaint: This patient came to emergency complaining of pain and soreness in the anterior abdominal wall. This pain was due, she said, to an embedded piece of metal. Physical exam: Mrs. J. was a little old lady with very volatile behaviour changes - she ranged from being agreable to irritable, demanding, and angry. Nevertheless she appeared quite healthy physically. Vital signs were stable and she was afebrile. Examination of H & N was normal; chest was clear, and CVS was within normal limits. On inspection of what was a benign abdomen there were several erythematous indurated papules one of which had a small piece of metal poking out. Mrs. J. denied knowing how it got there but suggested that she must have slipped and fell on a needle lying on the floor — a very unlikely theory. An attempt to remove the needle was initially unsuccessful. She was placed on cloxicillin prophylactically. Plain films of the abdomen showed several sewing-type needles in the abdominal wall and throughout the bowel. Ever since Mrs. J. lost her husband there had been a significant decrease in her ability to cope for herself. She no longer cooked and had even stopped her daily routines of personal hygiene. She was at times very angry at her family and very irritable. She had trouble sleeping and a poor appetite. Mental status exam: She was alert and oriented but very agitated. She looked somewhat messy. Her attitude towards the examiner was quite variable and unpredictable. Speech was somewhat rambling. Mood was euthymic although she did often state how sad she was about her husband's death. Perceptions were normal. Thought — rate: increased; form: normal; and content: anger and irritability towards her family. No suicidal ideation that she would admit to. Cognitive functioning was intact. She finally admitted her use of the needles and said it was a way to honour her husband. Diagnosis: she was diagnosed as having a masked reactive depression (2° to the death of her husband) and bizarre self-destructive behaviour. She was treated with amitriptyline (Elavil) and followed as an outpatient with good recovery.

CASE REPORT: A MONOSYMPTOMATIC HYPOCONDRIACAL DELUSION OF INTERNAL ORGANIC DECOMPOSITION AND DECAY TREATED WITH CLOMIPRAMINE

M.F. Pare, C. Booth*, A.J. Braganza, C. Chang and R.S.P. Kogucki

St. Joseph's Health Centre and the Department of Art as Applied to Medicine, University of Toronto, Toronto, Ontario

Mr. G.D. is a 55 year-old Italian man who presented to the emergency department complaining of (A) pain and a feeling of internal decomposition in the genital and suprapubic regions; (B) difficulty in achieving an erection and/or ejaculation during coitus or masturbation. History of the present illness: in 1985 Mr. G.D. underwent a TURP for prostatic hypertrophy. Afterwards he complained of an inability to ejaculate, yet he was able to urinate normally and achieve orgasm. He was investigated and found to indeed have retrograde ejaculation but no other abnormality was identified. Nevertheless, over the next few years he experienced frequent episodes of a bloating feeling in the pelvis, dysuria, and penile pain. He became convinced that the retained sperm from his retrograde ejaculation had developed into an internal abscess decomposing and decaying his pelvic organs. In addition, he complained that he was unable to achieve an orgasm. He was subsequently investigated on several occasions with a thorough urological workup including cystoscopy. No evidence whatsoever of any organic pathology was found. Past psychiatric history: Mr. G.D. had no past history of any other psychiatric difficulties prior to this problem. Social history: Mr. G.D. is a married, unemployed Italian tailor who lives with his wife, who works to support the couple. He has not been able to work since the beginning of the illness four years ago. Physical examination: was unremarkable; vital signs were normal, all systems were clear of signs and except for being moderately overweight, Mr. G.D. was found to have nothing wrong with him physically. Mental status examination: the patient was extremely agitated and emotionally distressed, yet was alert and oriented. In appearance he was a somewhat obese, anxious, red-faced man who was loudly moaning and grunting and groaning. He was pacing back and forth in his room; occasionally asking for help and bursting out crying. Clearly his behaviour was hysterical as he lamented his sorry fate to God and man. Occasionally he would slap his genitals roughly or punch the side of his head. He was convinced that there was an internal pelvic infection that could kill him. This unrealistic belief persisted despite repeated efforts to make him feel medically reassured. His mood was of extreme sadness and hopelessness. There were threats of suicide unless he was cured of this "disease". Speech was somewhat rapid and the volume was very loud. Thought form was essentially normal but his thought content indicated an obsessional and delusional thinking that centered on a single hypochondriacal issue. There were no other delusions or hallucinations. Cognitive functioning was completely intact. A diagnosis of major depression with monosymptomatic hypochondriasis was made. The patient was admitted to the psychiatry ward. He was again reassured that there was no physical basis for his beliefs and he was treated with pimozide (Orap) and clomipramine (Anafranil). He responded quite well and his delusional thinking decreased significantly over the next several days. He was discharged on pimozide and clomipramine. It is thought that clomipramine's action on obsessive delusional states is through its action at the serotonergic synapse where it indirectly increases synaptic transmission.

COMPUTER APPLICATIONS IN BIOETHICS FOR CANCER PATIENTS

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In the near future, computers will be used extensively to understand how patients select information, such as that provided in consent forms. Two different studies designed to develop computer programs for this purpose were undertaken. Both were written in Hypercard on a MacIntosh Plus. Patients answered questions by pressing only one button on the "mouse". The purpose of the first study was to develop an interactive program to discern patterns in patients' search for information. Information about a hypothetical clinical trial was presented, and patients could choose their own sequence of information bits from a menu — in effect, constructing their own consent forms. We also kept track of patients' sequence of information selection, so that ultimately we could trace a "map" of their information search process. In the second study, we used the same strategies to test Sox's[1] proposed approach for combining preferences for length and quality of life into a single outcome measure that could be used as a criterion in formal decision analysis. Hypercard was excellent for presenting information on screen with its editing, button, field and text features, but the data file manipulations were difficult. Training screens were given because many patients, especially the elderly, were first-time computer users. The number of refusals to use the computer was quite low. Assistance was available to patients, but seldom employed, because the programs were easy to use. In conclusion, with simple steps and some training screens, even first-time users could be self-taught in a short period of time to acquire information and answer questions.

[1]Sox H.C. Jr., Blatt M.A., Higgins M.C., Marton K.I. Medical Decision Making.
Butterworths, 1988.

CRANIO-ORBITO-ZYGOMATIC MEASUREMENTS FROM STANDARD CT SCANS IN UNOPERATED CROUZON AND APERT PATIENTS: COMPARISON TO NORMAL CONTROLS

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Cranio-orbito-zygomatic measurements taken from standard axial computed tomographic (CT) scans of unoperated Crouzon and Apert patients age two days to one year were compared to each other and to normal controls. Twenty-three Crouzon patients, 6 males and 17 females, and 15 Apert patients, 8 males and 7 females, were examined. Thirteen cranio-orbito-zygomatic variables were measured using dividers and a millimeter ruler on CT scans: measurements were repeated and the two results averaged. Means were computed for each sex, and these showed large standard deviations (SD) suggesting a high degree of variability within each syndrome. Coefficients of correlation were calculated for each variable which showed good reproducibility of measurements. An unpaired Student T-test between male and female groups within each syndrome revealed no significant difference. There was no significant difference between the pooled populations for each syndrome, suggesting that upper facial differences in these deformities are not demonstrable before one year of age. Comparison with normal data showed a significantly smaller zygomatic apparatus, shorter orbital sockets and larger interorbital angle. Statistically less significant differences were a shorter skull length, larger interorbital distance, and more excessive globe protrusion. Intercoronal, intertemporal and intercanthal distances were comparable to normal standards. Objective data taken from standard CT scans can allow comparison between specific syndromes and the normal population for any given patient.

NORMAL VALUES AND GROWTH TRENDS IN PAEDIATRIC CRANIO-ORBITO-ZYGOMATIC MEASUREMENTS

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Current diagnosis and surgical correction of craniofacial anomalies demands accurate quantitative and standardized points of reference. A retrospective study was undertaken to define normal values for a series of cranio-orbito-zygomatic measurements and to evaluate the growth pattern of the craniofacial region through axial computed tomographic (CT) scans. A comparison study of direct (dry skull) and indirect (CT scan) measurements was also carried out, and the results correlated closely. Fourteen measurements were taken from the CT scans of 458 skeletally normal patients between 1979 and 1989, and three distinct axial slices were used. These measurements were categorized by sex and then further subdivided into one year age groups ranging from the neonate to 18 years. Means, standard deviations, confidence intervals and growth trends were calculated for each. Initial univariate analyses indicated that the inter-orbital distance (corresponding to the cephalometric MO-MO), the most familiar of these measurements, has a strong linear relationship with age (regression coefficient = 0.72, P = 0.0001). There was also no significant difference between males and females for each age group studied ($P<0.05$). Other measurement groups displayed different patterns. Knowledge of the differential growth patterns of specific craniofacial regions allows for the optimal staging of reconstruction. The normal measurements at each 1 year age interval through skeletal maturity can be compared to those of the specific patient. This will be of assistance in the accuracy of diagnosis and the precision of corrective surgery.

ENHANCEMENT OF EXPRESSION OF THE HUMAN PARATHYROID HORMONE GENE IN ESCHERICHIA COLI

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Parathyroid hormone (PTH) is the major regulator of extracellular calcium concentrations. Recent studies suggest that this hormone has an anabolic effect on bone matrix synthesis. Thus, attempts have been made to generate sufficient quantities of PTH for clinical trials in treating osteopenic states. The human PTH (hPTH) gene has been cloned and expressed in *Escherichia coli* harbouring a plasmid (PUC8) containing a synthetic hPTH gene under the control of the *E. coli* lac promoter. However, the level of expression was not very high due to the relatively weak lac promoter. To improve expression, we inserted the hPTH gene into another plasmid (pKK223-3), which has a stronger promoter: the tack promoter. Also, a transcription termination codon was placed 3' downstream to the hPTH sequence to stabilize the gene. But expression was still not significantly improved because the distance between the starting codon and the ribosomal binding site was too great. Hence, to shorten this distance, the sequence between the tac promoter and the hPTH encoding region was recloned into a viral vector, M13mp8. Using this single-stranded DNA as the template, we were able to shorten the intervening sequence by primer-directed mutagenesis. As a result, expression of the gene was greatly enhanced and the products of expression of the plasmid were isolated by acid extraction follwed by HPLC. Amino acid analysis confirmed that the gene product sequence was indeed correct. Thus, we have achieved the successful construction of an expression plasmid which efficiently directs the synthesis of HPTH in bacteria.

THE EVALUATION OF VARIABLE GENE PROBES (VGP) TO STUDY THE RELATEDNESS OF BLOOD CULTURE ISOLATES OF STAPHYLOCOCCUS HEMOLYTICUS FROM TWO NEONATAL INTENSIVE CARE UNITS (NICU)

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During a 6-month period there were nine patients with *S. hemolyticus* bacteremia in the NICU of hospital-1 (H-1). Using plasmid profiling (PP) and restriction endonuclease analysis (REA) we characterized these isolates in addition to 9 other (8 blood and 1 skin culture) *S. hemolyticus* isolates from the NICU of hospital-2 (H-2). After REA and Southern hybridization we used VGP for B-lactamase, aminoglycoside inactivating enzyme APH (2")-AAC (6') I and methicillin resistance. VGP created 7 profiles (P1-P7). P1 included 7 bacteremic isolates from H-1 and 4 bacteremic isolates from H-2. All 11 proved to be identical by REA and PP. P2 included 2 bacteremic isolates from H-2, both of which were shown to be unrelated by REA and PP. P3 to P7 included one isolate each, which were also shown to be unrelated to all other isolates. Using VGP we were able to initially group strains of *S. hemolyticus* into similar types and then prove relatedness or unrelatedness by using REA and PP. In addition we were able to identify an epidemic strain of *S. hemolyticus* in two separate NICUs.

CARDIAC DISEASE-FREE SURVIVAL (CDFS) IN PATIENTS WITH THALASSEMIA MAJOR (TM) TREATED WITH SUBCUTANEOUS DEFEROXAMINE (DFO): AN UPDATE OF THE TORONTO COHORT

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Previously, we reported cardiac disease-free survival (CDFS) in transfused TM patients (pts.) begun on subcutaneous DFO after age 10 years (N. Engl. J. Med. 1985, 312:1600). Five years later, re-examination of the Toronto cohort by cardiac magnetic resonance imaging (MRI), exercise radionuclide scanning (MUGA), and compliance review, demonstrates wide heterogeneity within the "compliant" group. Overall, a decrease in compliance with age was observed, from 93.8±5% drug used (of that prescribed) at 10 years to 54.5±20% at 20 yrs. ($p<.005$). Of the 11 "compliant" Toronto pts., 2 are dead, 4 are maintained on digoxin and/or anti-arrhythmics, and 1 has heavy cardiac iron loading by MRI and abnormal diastolic function by MUGA. Four pts. have only mild abnormalities by MUGA and show only mild cardiac iron loading by MRI. Within the "compliant" group there was a wide range of DFO used (54-98% of that prescribed). Of the 12 "non-compliant" Toronto pts., 7 are dead (1 of a non-cardiac cause), 4 are maintained on cardiac medications, and 1 has moderate cardiac iron loading by MRI with an abnormal MUGA. Deceased pts. had received, to 1988, significantly less DFO than those living: 18±14 g/kg vs 42±25 g/kg body weight in 1988 ($p<.025$), despite equal doses prescribed (51±16 vs 57±21 g/kg, NS). Of 14 other pts. not analysed in 1983 but who initiated DFO at > 10 years of age, 2 are dead, 3 are on cardiac meds, and 8 have abnormal diastolic function by MUGA and cardiac iron loading by MRI, despite normal resting Echo. No correlation between DFO/kg received to 1988 and resting Echo was noted, but pts. who received < 90 mg DFO/kg body weight by 1988 had significantly more severe dysfunction by MUGA ($p<.02$) and more iron in the cardiac septum by MRI ($p<.05$). We conclude: 1) 45% of "compliant" pts. begun on DFO at 10 yrs. of age maintain CDFS five years after their first report; 2) "compliance" is a continuous, not a dichotomous variable in the evaluation of the long-term efficacy of DFO; 3) careful retrospective analysis indicates DFO compliance decreases with age but even good compliers may not enjoy CDFS if begun > age 10 years: 4) resting Echo used in most analysis of this type, including our own, remains normal in many pts. and is not a useful measure of CDFS.

MEASURING COVERT ATTENTION SHIFTS AFTER UNILATERAL STROKE: CORRELATION WITH HEMISPATIAL NEGLECT

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Bedside tasks used to assess neglect were standardized in 22 elderly control subjects and administered to 58 patients (26 left brain damaged (LBD), 32 right brain damaged (RBD)), consecutively admitted with acute unilateral hemisphere stroke confirmed on CT. A weighted score was derived from the most informative measures (drawing and copying a clock and daisy line bisections, and cancellation of 20 scattered lines, and 60 scattered designs). Twenty-eight subjects (12 RBD, 9 LBD, 7 controls) performed a cued reaction time (RT) task (Posner, 1982) to measure covert shifts in attention and to test the hypothesis that neglect correlates with impaired contralateral orientation of visual attention. In this computer task, lateralized cues were followed by targets in the same location (80% valid trials) or in the opposite location (20% invalid trials). We predicted elevated RT in contralateral targets on invalid trials in neglect patients irrespective of the side of lesion. The 13 patients without neglect showed no difference in ipsilateral or contralateral RT in both validity conditions. The 8 neglecting patients (5 RBD, 3 LBD) were significantly slower on contralateral RT in both validity conditions. The 8 neglecting patients (5 RBD, 3 LBD) were significantly slower on contralateral invalid trials ($F(1,7)=18,7$, $p<.005$), but not on the valid trials. Overall, contralateral RT was highly correlated with neglect score on invalid trials ($p<.0001$) and less so on valid trials ($p<.025$). This validates the scoring system and supports a role of impaired contralateral shifts of attention in neglect behaviour.

ESOPHAGEAL ACID PERFUSION: EXPLORATION OF THE LINK BETWEEN SENSORY STIMULATION, MOTOR CHANGES, AND SYMPTOMS

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The frequency and type of acid-induced changes of esophageal contractions, their significance, and their relationship to acid-induced symptoms remains unclear. To further study these issues 95 consecutive esophageal motility studies (EMS) with acid perfusion (AP) were assessed. Before AP, duration (DUR) and amplitude (AMP) of dry (DS) and 5cc-wet (WS) swallow waves were measured. AP was then instituted for up to 20 min. The time of onset to symptoms and to changes in AMP (> 200mmHg) and/or DUR (>8 sec) of DS waves at 5 cm above the LES was recorded. The AMP and DUR of DS were measured. AP was discontinued until symptoms disappeared or for up to 10 min, when AP was reinstituted and measurements repeated. Results: On initial AP, a) symptoms occurred in 90 patients, motor changes in 77 patients, and both in 74 patients. Sixteen patients had symptoms alone; only 3 had motor changes alone; b) an increase in DUR was seen in 74 patients, and of AMP in only 28; c) in subjects with symptoms only, lower esophageal sphincter pressure (LESP) was abnormally low (x = 8.8 mmHg) and esophageal contraction AMP before AP was low; in those with motor changes ± symptoms, LESP was normal (x = 14.2 mmHg) and contraction AMP normal or high; d) the time to onset of symptoms and motor changes with the second AP (x = 90 sec for both) was much shorter than to onset with the initial AP (x = 365 and 376 sec respectively). When symptoms and motor changes were present, their onset occurred at approximately the same time. Conclusions: 1) On esophageal AP: a) motor changes, especially an increase in DUR, are very common, b) motor changes are almost always associated with the presence of symptoms, c) patients with symptoms only have low LESP and contraction AMP, and probably more severe reflux disease; 2) with acid exposure, the esophagus and its neural pathways become highly sensitized to readily produce both symptoms and motor changes on subsequent acid challenge. This has implications in regard to those central and peripheral neural mechanisms that control esophageal contractions with swallowing and mediate the production of symptoms.

DOES SWAN GANZ CATHETERIZATION INFLUENCE ICU MANAGEMENT FOLLOWING ELECTIVE AORTIC SURGERY?

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The postoperative management of elective aortic reconstruction has progressively involved more invasive monitoring, pharmacological interventions, and routine ICU admissions. The purpose of this study was to assess the usefulness of Swan Ganz catheterization (SGC) in directing patient care. We have reviewed all patients admitted to the Surgical Intensive Care Unit following elective infrarenal aneurysm repair, or repair of aorto-iliac occlusive disease, from 1985 to 1988. There were 368 patients; 274 were instrumented with an SGC, usually at the discretion of the anaesthetists. There was no significant difference in age, or increased incidence of renal or pulmonary disease in those catheterized. However, there was an increased incidence of ischemic heart disease in those patients instrumented with an SGC. There was no significant difference in intraoperative crystalloid replacement, or urine output. The blood transfusion requirements were significantly greater in the SGC group ($p<0.005$). The use of vasodilating agents, for afterload reduction and vasopressors was greater in patients with SGC, ($p<0.05$). There was a significant difference in fluid balance at 24 hours between those with SGC (6300 ± 202) and those without SGC (5165 ± 269), ($p<0.05$). There were 9 mortalities (8 with SGC). In summary, Swan Ganz-directed care was associated with increased fluid administration, but no other apparent beneficial interventions.

DIFFERENTIAL DIAGNOSIS IN DEMENTIA: A SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY STUDY USING TECHNETIUM-99M HMPAO

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The differential diagnosis and staging of dementia in various neurodegenerative diseases has proved to be difficult for a variety of reasons. However, early and accurate diagnosis is essential for proper clinical management and the direction of research efforts. In this regard, we have been evaluating regional cerebral perfusion by single photon emission computed tomography (SPECT) using Technetium-99m HMPAO. Dementia patients were injected intravenously with Technetium-99m HMPAO and its uptake and distribution were recorded. The acquired data were then processed to generate images in the coronal, sagittal and transaxial planes. These were analyzed visually as to technical adequacy of the study and deficits in cortical perfusion. Optimization of the reconstruction process yielded images of relatively high resolution which could be reliably interpreted. We present here a detailed scheme to assess these deficits on a semi-quantitative basis relative to cerebellar perfusion. We observed characteristic patterns of decreased cortical perfusion in various types of dementia including Alzheimer's, multiple infarct, and Pick's. In many cases, we found that perfusion deficits are detectable by SPECT whereas both cranial computed tomography (CT) and magnetic resonance imaging (MRI) fail to do so. Thus Technetium-99m HMPAO-SPECT appears to be a promising modality for the clinical management of dementias. In addition, SPECT scanning is easily performed using conventional equipment and offers in this case a low-cost alternative to techniques such as positron emission tomography.

EFFECT OF CAFFEINE ON VENTILATORY RESPONSES TO HYPERCAPNIA, HYPOXIA AND EXERCISE IN HUMANS

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The effect of oral caffeine on resting ventilation (V_E), ventilatory responsiveness to progressive hyperoxic hypercapnia (HCVR), isocapnic hypoxia (HVR) and moderate exercise (EVR) below the anaerobic threshold was examined in 7 healthy adults. Ventilatory responses were measured under three conditions; control (C) and following ingestion of either 650 mg caffeine (CF) or placebo (P) in a double blind randomized manner. None of the physiological variables of interest differed significantly for C and P conditions, $p > 0.05$. Caffeine levels during HCVR, HVR and EVR were (mean ± SD umoles/L) 69.5 ± 11.8, 67.8 ± 10.8 and 67.8 ± 10.9 respectively, $p > 0.05$. Metabolic rate at rest and during exercise was significantly elevated during CF as compared to P. An increase in V_E from 7.4 ± 2.5 L/min P to 10.5 ± 2.1 L/min CF, $p < 0.05$, was associated with a decrease in end tidal carbon dioxide tension from 39.1 ± 2.7 Torr P to 35.1 ± 1.3 Torr CF, $p < 0.05$. Caffeine increased the HCVR, HVR and EVR slopes (mean increase; 28 ± 8%, 135 ± 28%, 14 ± 5%, respectively) as compared to P; $p < 0.05$ for each response. Increases in resting ventilation, HCVR and HVR slopes were associated with increases in tidal volume whereas the increase in EVR slope was accompanied by increases in both tidal volume and frequency of breathing. Our results indicate that caffeine increases resting ventilation and chemosensitivity to CO_2 inhalation, hypoxia and CO_2 production during exercise below the anaerobic threshold.

REDUCTION OF MYOCARDIAL INFARCT SIZE BY DIETARY ALPHA TOCOPHEROL

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Alpha tocopherol (AT) has been shown to reduce myocardial ischemic injury if infused immediately before an ischemic insult. AT probably protects myocardium by preventing free radical lipid peroxidation. Water-soluble AT analogs designed for rapid cell uptake are currently being studied for peri-operative use. However, the lipid solubility of AT has a potential advantage that has not been exploited: dietary supplementation could be used to accumulate high tissue levels of AT in patients awaiting cardiac procedures. We sought to determine whether prior dietary supplementation with AT could reduce experimental myocardial infarct size. New Zealand white rabbits (3.5-4.0 kg) were fed standard laboratory feed and water ad libitum for 10 days, plus either 800 iu/day d-alpha tocopherol (AT Group), or no supplement (Control Group). Rabbits then underwent either 60 min or 180 min of LAD ligation, followed by 6 hrs of reperfusion. The area at risk was identified with colloidal carbon and areas of necrosis with triphenyl tetrazolium chloride and histology. In the 60 min ligation study, the control group had 30.5% ± 4.0% (mean ± S.D.) necrosis of the area at risk but the AT group had no necrosis (n=5 per group, $P < 0.0001$). In the 180 min ligation study, the control group had 84.0% ± 11.1% necrosis of the area at risk whereas the AT group had 21.2% ± 6.7% (n=5 per group, $P < 0.0001$). We conclude that dietary supplementation with AT at a dose of approximately 200 iu/kg/day can significantly reduce myocardial infarct size.

DECREASED CD23 EXPRESSION ON EPSTEIN-BARR VIRUS TRANSFORMED B-CELLS FROM PATIENTS AFFLICTED WITH THE WISKOTT-ALDRICH SYNDROME

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The Wiskott-Aldrich Syndrome (WAS) is a recessive X-linked primary immunodeficiency disease where both humoral and cellular immunity are impaired. A significant decrease in platelet size and number is also found in this disorder. CD23/Fc RII is a single polypeptide chain of 47 kd that is expressed on the surface of IgM/IgD positive B-cells but not Pre-B-cells or isotype-switched IgG, IgA, or IgE B-Cells. CD23 is known to be a low affinity receptor for the Fc portion of IgE as well as being an autocrine B-cell growth factor when released from the cell surface as a soluble 25 kd fragment. Thus, it is believed to be an important antigen in B-lymphocyte differentiation and/or proliferation. In Epstein-Barr Virus (EBV) transformed B-cells there is a high density of CD23 surface expression. We found that there was a significant but varied decrease of CD23 expression in four different EBV transformed WAS B-cell lines. We also found preliminary evidence indicating that this corresponded to a decreased level of the released soluble 25 kd fragment in the supernatant of WAS transformed B-cells. Several other surface antigens were also tested, with none showing any significant differences in expression. These results suggest that decreased CD23 surface expression and its associated decrease levels of soluble CD23, given the possible functional importance of CD23, may contribute to the impaired humoral immunity seen clinically in WAS patients.

HYPOXIA INDUCES DNA OVERREPLICATION AND ENHANCES THE METASTATIC POTENTIAL OF MURINE TUMOR CELLS

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Cultured cells subjected to oxygen deprivation have been shown to undergo anomalous DNA synthesis, which can result in DNA overreplication and the generation of cellular variants (Rice, G.C., et al., 1986, Proc. Natl. Acad. Sci. 83:5978). In our studies, murine tumor cells were exposed in vitro to severe hypoxia and then tested for their ability to form experimental metastases by i.v. injection into groups of mice. Upon reoxygenation, cells experienced a transient, yet dramatic, increase in metastatic potential. Flow cytometric analysis confirmed that hypoxia and reoxygenation induced cell cycle perturbations and DNA overreplication in these tumor cell lines. Fibrosarcoma cells with overreplicated DNA isolated by fluorescence-activated cell sorting were highly efficient at forming pulmonary metastases, although cells with normal (2-4C) DNA content in populations treated with hypoxia were also markedly more metastatic than oxidated populations. These results further suggest a role for gene amplification in cancer metastasis, and support the hypothesis that hypoxic conditions existing in regions of solid tumors may promote cellular heterogeneity and tumor progression.

CYCLIC RESPIRATORY MOTION IS NOT IMPORTANT TO MAINTAIN LUNG SURFACTANT PROPERTIES

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We examined the effect of cyclic lung stretch on surfactant function by comparing two different modes of ventilation, conventional mechanical ventilation (CMV) and constant flow ventilation (CFV), a technique in which the animal is ventilated without any chest wall movement. Four dogs in each group were ventilated for 8 hours. At the end of this period a bronchoalveolar lavage of the upper and lower lobes in each lung was performed, and samples were taken for surfactant and protein analysis. The level of arterial oxygenation on 40% oxygen was slightly higher on CMV (186±15 mmHg) than on CFV (164±24 mmHg; $p<0.05$) at the end of the experiment. All lavage samples reached a minimum surface tension of 15 mN/m. There were no significant differences in the upper and lower lobe parameters studied; thus, they were pooled in the final analysis. The lipid phosphorous concentrations were similar in both groups (CMV: 0.05±0.01 uM/ml; CFV: 0.06±0.04 uM/ml; $p>0.05$). The total protein concentrations were also not different (CMV: 1.94±3.44 mg/ml; CFV: 1.43±2.82 mg/ml; $p>0.05$). The content of phospholipids were higher than normal but there were no differences between CMV and CFV (8.15±0.52 % vs 8.36±2.26 % respectively; $p>0.05$). Therefore, the removal of cyclic lung stretch by CFV does not affect the surfactant composition of normal lungs.

PAEDIATRIC MYOCARDIAL PROTECTION: AGE-RELATED DIFFERENCES IN MYOCARDIAL BUFFERING CAPACITY

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Continued high mortality and morbidity associated with newborn cardiac surgery despite the use of successful adult myoprotective techniques suggests different myocardial sensitivities between adult and newborn hearts to stress. Buffering capacity (BC) is a measure of the ability of a system to resist changes in pH when acid or base is added. The present study was undertaken to assess potential differences in myocardial BC between adults and neonates by testing in vitro BC, and relating lactate and pH values. Newborn (3 day old) piglets (n=10) and adult (4-5 month old) pigs (n=10) were anaesthetized and ventilated. A midline sternotomy exposed the heart and left and right ventricular biopsies were taken. After excision of the heart, additional biopsies were taken at 10, 20 and 60 minutes. The biopsies were assayed for pH, lactate levels, and BC. BC, expressed in units of umol H^+/g wet weight tissue/pH unit, was determined by titrating homogenates of the biopsy tissue with acid. While the slopes of the lactate-pH plots were almost identical for adult and neonatal RV tissue, the LV slope differed between the neonate and adult, suggesting differences in neonatal and adult LV BC. The BC values determined by titration showed that adult LV BC (43.3± 2.4) was significantly higher than adult RV, neonatal LV, and neonatal RV, which were similar (36.8±3.3, 36.9±3.2, and 37.1± 2.3 respectively). The increased vulnerability of neonatal ventricular tissue to acid-base disturbances, compared to adult LV, may be one reason why neonatal hearts do not respond as well to adult myoprotective techniques. This should be considered in order to improve myocardial protection in this special group of patients.

IMPROVED TWO-DIMENSIONAL NMR METHODS FOR CHARACTERIZATION OF SECONDARY METABOLITES OF MEDICINAL PLANTS

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In many of the less-developed countries of Central and South America, Asia and Africa, there is a well established traditional or folklore medicine, mainly based on plant extracts. For example, in Mexico there is historical evidence for the continuous use of the same plants for the same medicinal purposes for as long as 1000 years. Many compounds which are used in modern medicine (e.g. aspirin, morphine, quinine, digitalis, vincristine and vinblastine) were first isolated from medicinal plants and these plants are still the single largest source of pharmacologically active compounds. Phytochemical investigations of medicinal plants require sophisticated and sensitive analytical methods to allow rapid identification of known compounds and unambiguous structural characterization of new compounds. High resolution nuclear magnetic resonance (NMR) spectroscopy is particularly useful in this regard. My Ph.D. research involved the development of a series of new two-dimensional NMR techniques for characterization of complex natural products. These new experiments (or "pulse sequences") are illustrated using kauradienoic acid as an example. This diterpene was isolated from the plant *Montanoa tomentosa*. This plant, known as Zoapatle (or "plant of the women" in the Toltec dialect), is still widely used as an abortifactant in Mexico and kauradienoic acid is one of the active ingredients. The unambiguous structural and spectral characterization of this compound and other natural products by 2D NMR will be illustrated. The new pulse sequences give improved sensitivity and/or resolution as compared with previous experiments as well as improved information content. With further developments, it should be possible to carry out a full characterization of an unknown natural product in as little as 24 hours with no more than 1-2 mg of sample. This will greatly facilitate phytochemical investigations of medicinal plants and consequently improve the chances of isolating more pharmacologically useful compounds.

THE EFFECT OF SECTIONING THE TRIGEMINAL SENSORY ROOT ON THE PERIODONTALLY-INDUCED JAW-OPENING REFLEX

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The experiment was designed to determine the pathway taken to the brain-stem by periodontal afferents responsible for the digastric jaw-opening reflex induced by tooth-tapping. Cutting the trigeminal sensory roots of anaesthetized decerebrate cats eliminated the ipsilateral periodontally-induced reflex, although the stretch reflexes of the jaw-closing muscles were undiminished. These results suggest that periodontal afferents causing the jaw-opening reflex reach the brain-stem through the trigeminal sensory root, and confirm that muscle spindle afferents travel through the trigeminal motor roots.

H3 CYS-110 IS IN AN ALTERED CONFIGURATION IN NUCLEOSOMES ASSEMBLED AT PHYSIOLOGICAL IONIC STRENGTH

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Nucleosome particles can be assembled when chicken erythrocyte core histones are mixed with salmon sperm DNA at physiological ionic strength (0.15 M NaCl) and at 0.6 M NaCl, which are subsequently treated with micrococcal nuclease. These core particles are indistinguishable when assayed for histone composition, hydrodynamic behaviour, thermal denaturation, circular dichroism but distinct when analyzing their 2-iminothiolane cross-linking patterns and fluorescence quenching of fluorescein-labeled histone H3 [Ellison, M.J. and Pulleyblank, D.E. (1983) J. Biol. Chem. 258, 13314-13320]. Here we show that the DNAse I digestion pattern is also indiscernible between the nucleosome particles. However using both cleavable (N-(4-azidophenylthio)pthalimide) and non-cleavable (p-azidophenacyl bromide) photo-affinity reagents attached to the unique histone H3 cysteine, we were able to specifically cross-link histones within particles and detect a configurational difference in particles annealed at 0.15 M NaCl. Cross-linked H3-H3, H3-H2B and H3-H4 histone dimers were prominent when particles were prepared in 0.15 M NaCl but only H3-H3 histone dimers were formed in significant yield when the particles were prepared in 0.6 M NaCl. Cyanogen bromide peptide mapping revealed that Cys-110 of histone H3 is cross-linked to the 18 amino acid C-terminal end of H4 and to the 66 amino acid C-terminal half of H2B. These results confirm that the histone H3 is in an altered arrangement in a population of nucleosome particles that were annealed at physiological ionic strength.

RELATIONSHIP OF THALAMIC NEURONAL RESPONSES AND MICROSTIMULATION EVOKED SENSATIONS ELICITED AT THE SAME SITES IN MAN

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The use of both microstimulation and microrecording during stereotactic thalamotomy procedures provides a unique opportunity for correlating evoked thalamic responses with sensations evoked by electrical stimulation at the same site. In the present study, thalamic ventrobasal complex neurons responding to sensory stimulation were recorded at 518 different sites in a total of 80 different electrode trajectories in 22 patients undergoing stereotactic thalamotomy for motor disorders. Single and multi-unit recordings have shown thalamic regions to respond optimally to different modes of somatic stimulation where the voluntary zone (responses to voluntary movements), kinaesthetic zone (responses to joint movement and pressure to muscles), deep zone (responses to mechanical stimulation of deep tissues) and cutaneous zone (light mechanical stimulation) could be distinguished. In the latter zone, most of the neurons had small receptive fields on the digits, lips and face. There were fewer neurons with receptive fields on other body regions such as leg, arm and torso and their receptive fields were larger. Stimulation at all of these recording sites (1 second, 300Hz, trains of 0.1ms pulses, <25uA) induced sensations (usually tingling) referred to a body part (projected field). In the well represented hand and face regions in the cutaneous zone, microstimulation usually resulted in identical or overlapping projected fields and receptive fields. However, when the receptive fields were on less well represented regions of the body such as torso or leg, which was more common in the deep zone, the projected field was frequently different from the receptive fields of the neurons recorded at that site. The current thresholds necessary to evoke sensations were also usually higher at those sites where there was a large mismatch between the receptive field and projected field. These results suggest that functionally segregated regions exist in the ventrobasal complex. Furthermore, these findings indicate that the receptive and projected field sizes are inversely related to the degree of representation of that body region and that there is usually an excellent correspondence between the neuronal receptive fields and the projected fields in well represented regions.

CIS AND TRANS ACTIVITY OF THE RZCAT-1 RIBOZYME IN VIVO

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RNA catalysis (self-cleavage) has been demonstrated in vitro for the satellite RNAs of the tobacco ringspot virus (sTobRV) hammerhead structure. The demonstration that the "hammerhead" sequence could be modified to cleave any desired GUC containing sequence in the trans conformation in vitro suggests possibilities for control of gene expression using ribozymes. We have studied the ability of the RzCat-1 ribozyme (Haseloff & Gerlach, Nature 334, 585 (1988)) to control expression in vivo (*E. coli*) of chloramphenicol acetyl transferase (CAT). The ribozyme was placed in cis and trans conformations with respect to its target sequence near the 5' end of the CAT gene in amp^r plasmids. In cis, RzCAT-1 was inserted 3' to the CAT gene. These plasmids, once transformed into Hb101 *E. coli*, allowed us to examine RzCAT-1's activity in vivo. Transformants containing RzCat-1 and cis plasmids were found to exhibit a lag when grown in the presence of chloramphenicol (Cm), indicating that the ribozyme was efficiently cleaving the CAT transcript, thereby suppressing Cm resistance.

PHYSIOLOGIC SIGNIFICANCE OF ELECTROGRAM SIGNAL CHARACTERISTICS DURING ATRIAL FIBRILLATION: SIMULATED ELECTROGRAMS IN A COMPUTER MODEL

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Previous studies of detection algorithms for atrial fibrillation (FIB) from electrograms (EG) have focused on rate, density (probability density functions) and frequency domain measures. However, little is known about the physiologic determinants of these measures. Simulated EG were calculated from a modification of Moe's computer model of atrial FIB by simulating a bipolar catheter above a 100x100 sheet of hexagonal elements. These EG closely resemble EG from human atrial FIB. Atrial rate was 488 to 592 beats/min (mean ± sd 546±29), density was 22 to 40% (30±6), and median frequency was 4.2 to 8.4 Hz (7.6±1.4). All simulated EG met reported criteria for detection of human FIB. The relationship between these measures from the EG and FIB physiology was investigated by manipulating the refractoriness of model elements. Number of wavelets was 15 to 60 and wavelength was 30 to 83 mm (45±6). As refractoriness increased, FIB organized and terminated (as reported by Moe); concomitantly rate changed little, but density increased and median frequency decreased. EG density was correlated (r=0.67) with the number of wavelets present in the model. Median and peak frequencies of the simulated EG were strongly correlated (r=0.79, r=0.99) with the refractory period of model elements within the field of the electrode. Conclusions: quantitative measures of EG during FIB vary to reflect underlying arrhythmia physiology. Density relates to the number of wavelets within the bipole field. Median (or peak) frequency is a measure of tissue refractory periods during FIB.

CHARACTERIZATION AND SITE-DIRECTED MUTAGENESIS OF A GENE ENCODING A DEFECTIVE FOLYLPOLYGLUTAMATE SYNTHETASE-DIHYDROFOLATE SYNTHETASE IN *ESCHERICHIA COLI*

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Polyglutamylation of folates is important for the regulation of one-carbon metabolism and essential for the activity of some folate-dependent enzymes. The polyglutamylated form of the antifolate chemotherapeutic drug, methotrexate, has been shown to be the active form of drug in vivo. An understanding of the enzyme that adds glutamate to folates may lead to the development of rational inhibitors with clinical relevance to cancer chemotherapy. The cloned gene of a mutant folylpolyglutamate synthetase (FPGS) from the SF_4 strain of *E. coli*, which has an Ala to Thr mutation at amino acid 309 (Ala309Thr), was mutagenized using oligonucleotide primed mutagenesis to replace Ala 309 with various other amino acids. Site-directed mutants generated were used to complement the genetic lesion in the original SF_4 mutant strain. Three mutants, Ala309Gly, Ala309Ile and Ala309Val all allow SF_4, which is auxotrophic for methionine, to grow on minimal medium. The wild-type gene (Ala309) and the original mutant gene (Ala309Thr) also complement SF_4. Other site-directed mutants Ala309Phe, Ala309Gln, Ala309Arg, Ala309Glu, Ala309Leu and Ala309Trp were unable transform SF_4 to methionine prototrophy. Thus it appears that small, hydrophobic amino acid side chains allow complementation to occur, whereas large and/or charged side chains prevent complementation. Activities of the mutants determined by enzyme assays confirm these data. These results indicate that Ala 309 may not be involved in catalysis of the FPGS reaction, but instead may play a role in determining the specificity and affinity for the binding of the folate substrate.

BACTERIAL TRANSLOCATION (BT) INDUCES MONOCYTE PROCOAGULANT ACTIVITY (PCA)

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Several stimuli which induce Multiple Organ Failure (MOF) in man have been shown to induce BT in the gut in experimental models, but a causal relationship between BT and end organ dysfunction remains to be established. Microcirculatory thrombi in the liver and lung are thought to be related to organ dysfunction in MOF. The purpose of these studies was to determine whether BT, in the absence of other stimuli, could induce monocyte (MO) PCA as a potential mechanism for microcirculatory fibrin deposition. Male Wistar rats were monoassociated with streptomycin-resistant *E. coli* C25 by oral inoculation following gut decontamination with bacitracin and streptomycin. PCA was measured by the ability of mesenteric lymph node (MLN) and portal vein blood (PVB) mononuclear lysates to shorten the clotting times of recalcified plasma. Clotting times were converted to PCA using a rabbit thromboplastin standard.

	n	BT rate	Bacteria/ 0.1gMLN (log10CFU)	PCA % control MLN	mean +SEM PVB
Control	17	6%(1/17)	—[a]	100.0± 5.6	100.0± 4.9
Mono-associated	31	90%(28/31)	1.81±0.16	209.8±28.3[b]	131.4±12.4[c]

[a] 2.32 in 1 rat
[b] $p<0.001$ vs control, by unpaired t-test
[c] $p<0.05$ vs control

In 28/31 monoassociated rats, MLN PCA was increased as compared to that in control rats sacrificed the same day. This difference was not due to a higher percentage of MOs in the MLN cells of monoassociated rats (9.1±1.4% vs 9.4±0.9% in controls, n=8), but rather to activation of fixed tissue MOs, presumably by sustained exposure to *E. coli* C25 and/or their products. In 18/31 monoassociated rats, PVB PCA was increased as compared to control, suggesting that exposure of circulating MOs to *E. coli* C25 and/or their products was sufficient to induce PCA expression in ~50% of animals. Thus, BT per se can activate tissue and circulating MOs for enhanced PCA expression in rats. MO-mediated microvascular fibrin deposition in solid organs represents a potential mechanism by which BT could contribute to the pathogenesis of MOF.

FAILURE OF DEFEROXAMINE TO LIMIT INFARCT SIZE IN EXPERIMENTAL MYOCARDIAL INFARCTION

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Deferoxamine (DF), by limiting hydroxyl radical-induced injury, has been shown to reduce infarct size when given prior to coronary occlusion but not when given at the time of reperfusion. In order to clarify this issue, we simulated the clinical situation by administering DF (15 mg/kg bolus and infusion) or control solution starting at 45 min prior to reperfusion in 13 anesthetized open chest dogs undergoing 2 hr of circumflex occlusion and 4 hr of reperfusion. Microsphere blood flow (BF) measurements (at 1 hr of occlusion and 4 hr of reperfusion, in ml/min/g) and infarct size are displayed below in the 2 groups (mean ± SEM).

	DF(n=7)	Control (n=6)
Risk/LV (%)	51 ± 4	51 ± 2
MI/Risk (%)	18 ± 4	23 ± 7
Occlusion BF:		
Subendocardial	0.04 ± 0.01	0.07 ± 0.03
Subepicardial	0.33 ± 0.07	0.31 ± 0.08
Reperfusion BF:		
Subendocardial	1.05 ± 0.29	1.05 ± 0.29
Subepicardial	1.68 ± 0.31	1.71 ± 0.30

Despite trends towards smaller infarcts in the DF group, these differences did not reach statistical significance. In addition, treatment with DF did not improve reflow during reperfusion in these animals. We conclude that DF does not salvage myocardium when given 45 min prior to reperfusion and thus, may not be a useful clinical therapy for patients undergoing thrombolysis.

EFFECT OF AFFERENT RENAL NERVE STIMULATION ON PARAVENTRICULAR NUCLEUS NEURONS

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Afferent renal nerves (ARN) are thought to be involved in hypertensive processes because of their influence on neuronal circuits that control arterial pressure (AP) and body fluid balance. In particular, neuronal circuits involving the paraventricular nucleus of the hypothalamus (PVH) can alter the development of hypertension. The relationship between ARN and PVH neurons was investigated by a series of experiments. In the first series, plasma levels of arginine vasopressin (AVP) and oxytocin (OXY) were measured in conscious baroreceptor-intact rats during ARN stimulation. ARN stimulation produced approximately 4-fold and 2-fold increases in plasma AVP and OXY respectively. In the second series of experiments, single-unit recordings of AVP and OXY PVH neurons were obtained to determine the response of these neurons to ARN activation. ARN stimulation excited 73% of AVP neurons and 30% of OXY neurons. Finally, the response of AVP and OXY neurons to selective activation of renal mechanoreceptors and chemoreceptors was investigated. Both AVP and OXY neurons responded to renal ischemia, renal venous occlusion, and intrarenal infusions of bradykinin, capsiacin, adenosine, and sodium cyanide, however not all neurons responded and a greater percentage of AVP neurons were excited than OXY neurons. These data suggest that ARN and the PVH are important components of a neuronal circuit that functions in cardiovascular regulation. Additionally, these data demonstrate that renal receptor populations contribute to the control of AVP and OXY release into the circulation.

CHANGES IN EXTRACELLULAR POTASSIUM EVOKED BY GABA AGONISTS IN THE HIPPOCAMPAL SLICE

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The effects of GABA (gamma-aminobutyric acid) and related compounds on extracellular [K^+] were examined using ion-selective microelectrodes in slices of guinea pig hippocampus. Bath applications of GABA (0.1-10 mM) resulted in reversible, dose-dependent increases in [K^+]o, which were greatest in the pyramidal cell layer, characterized by an ED_{50} of 3mM and a maximal increase of 1.8 mM. The GABA-agonist THIP (0.1-1 mM) evoked changes in [K^+]o similar to those observed in the presence of GABA, while baclofen (0.01-1 mM) caused only small (<0.5 mM) changes. Bicuculline (100 uM) and picrotoxin (100 uM) reduced the maximal GABA-evoked response by 25%. Pentobarbital (100-1000 uM) and ethanol (20-100 mM) also caused dose-dependent increases in [K^+]o of up to 1.5 mM and potentiated both GABA- and THIP-evoked changes. These data strongly suggest that GABA-evoked accumulations of extracellular K^+ are due primarily to a GABA-receptor mediated increase in K^+ conductance although Na/K and K/Cl exchange and co-transport may also contribute.

COMPARISON OF AN EQUIPOTENT GLUCOSE LOWERING DOSE OF INSULIN AND INSULIN-LIKE GROWTH FACTOR I IN TOTALLY DEPANCREATIZED DOGS

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The present study was undertaken to investigate the effects of an equipotent glucose lowering dose of insulin and insulin-like growth factor I (IGF-I) on metabolic substrates and tracer determined glucose kinetics in diabetes. Fourteen experiments (7 with insulin and 7 with IGF-I) were carried out in 8 fasted depancreatized dogs. Steady state hyperglycemia (10 mmol/L) was maintained by a sub-basal intraportal infusion of insulin which maintained a porto-peripheral gradient of insulin. IGF-I or insulin was administered peripherally as a bolus followed by a 90 minute infusion period and a 50 minute recovery period. The equipotent doses given were: IGF-I 2.6 nmol/kg ± 57.4 pmol/kg/min infusion; and insulin 0.07 nmol/kg ± 6.4 pmol/kg/min infusion. Plasma glucose declined by 44±5% with both insulin and IGF-I, to 5.8 mmol/L and remained in the normoglycemic range during the recovery period. With the peripheral insulin infusion, insulin plateaued at 280 pmol/L and with the IGF-I infusion, no changes in plasma IRI were seen. Inhibition of glucose production was greater with insulin (45±11%) than with IGF-I (27±9%) and consequently the metabolic clearance rate of IGF-I was increased greater with IGF-I (120±43%) than with insulin (92±49%). Plasma lactate increased up to twice basal with IGF-I, declining before the end of the infusion while with insulin, the rise in lactate was not significant. Glycerol declined significantly with both IGF-I (29±14%) and insulin (54±9%) but significantly more with insulin. Pyruvate increased more than 2-fold and beta-hydroxybutyrate decreased by more than 50% with both IGF-I and insulin administrations ($p<0.05$). Alanine declined significantly throughout the infusion and the recovery periods with no significant difference between IGF-I and insulin administrations. Conclusions: 1) IGF-I had no effect on insulin clearance. 2) IGF-I was 9% as potent as insulin in lowering plasma glucose. 3) Differential effects of IGF-I and insulin on glucose kinetics indicate a greater peripheral effect of IGF-I and a greater hepatic effect of insulin.

DEVELOPMENT OF STRIATAL COMPARTMENTALIZATION: THE ROLE OF VENTRICULAR ZONE EVENTS

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The division of the striatum into patch and matrix compartments is conserved in different mammalian species (rodents, cats, monkeys and humans). The patch compartment consistently comprises approximately 15% of the total striatum, in spite of enormous differences in total striatal size across species. The patch and matrix compartments, like the deep and superficial layers of the cortex, are born at different times during development. The patch compartment and the deep layers become postmitotic early and the matrix compartment and superficial layers become postmitotic later in embryogenesis. Indeed, we hypothesize that two distinct stem cell populations may give rise to forebrain neurons, one producing striatal patch and deep cortical layers, and the other producing striatal matrix and superficial cortical layers. Intraocular transplants of embryonic striata maintain patch and matrix-compartments proportional to the size of the two populations at the time of removal of the graft. This suggests that commitment to a striatal compartment is an early developmental event. If compartmental commitment does occur while the precursor neurons are still proliferating, then evidence for this heterogeneity within the striatal ventricular zone must be present. The expression of cellular oncogenes, which are thought to be responsible for promoting growth and differentiation, is localized in subsets of radial glial cells at embryonic day 18 in the rat ventricular zone. These areas of oncogene staining coincide with increased levels of proliferation, as judged by ^3H-thymidine labelling. This suggests that some ventricular zone cells have shorter cell cycle times than others. To test the idea that two neuronal populations with different cell cycle times give rise to the patch and matrix compartments, we are presently using double DNA labelling synthesis experiments in order to selectively mark the population with the shorter cell cycle times. Lineage studies, using a replication-deficient retrovirus and chimeric animals, also support the hypothesis that separate precursors exist for each of the striatal compartments.

THE TOXIC EFFECTS OF DIRECT-CURRENT STIMULATION ON AN INTACT RAT SPINAL CORD

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There has been considerable work done focusing on the beneficial effects of direct current (DC) electrical stimulation; however information concerning associated undesirable effects is lacking. In the present study, the unwanted effects of chronic in vivo DC stimulation on an intact rat spinal cord are examined. Two rats underwent a C7-T1 laminectomy and epidural implantation of a 50uA stimulator. Clinical neurological function was assessed by the inclined plane technique and observations of upper and lower limb function as well as respiratory pattern. Postmortem, both cords were examined grossly and then serially sectioned for histology. One of the cords was selected for computer 3-dimensional reconstruction and volumetric analysis. Clinically, both rats evidenced decreased inclined plane scores, progressive limb dysfunction, and respiratory distress. There was also evidence of surface and internal pathological changes in the cord. On examination both cords showed evidence of profound cavitation at the anode site. There also appeared to be considerable haemorrhage, loss of grey and white matter tissue, protein deposition along with accompanying inflammatory response, and myelin disintegration within the cord. These data suggest that 50uA delivered to the rat spinal cord can result in harmful effects.

ESTROGEN-INDUCED ALTERATION OF ADP-RIBOSYLATED PROTEIN EXPRESSION IN THE ANTERIOR PITUITARY BUT NOT IN THE STRIATUM OR UTERUS

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Estrogen (E_2) treatment reliably results in hyperplastic growth of anterior pituitary (AP) lactotrophs. We have previously shown attenuation of adenylate cyclase activity in AP after E_2 treatment, with blunted responses to stimulation by VIP and inhibition by bromocriptine. The effect of E_2 on the post-receptor mediators of function, guanine nucleotide binding proteins, were studied. Ovariectomized female rats were treated with E_2 for 21 days. The studies were conducted in accordance with the established guidelines for animal research. The guanine nucleotide binding proteins were studied using bacterial toxins to catalyze ADP-ribosylation. Cholera toxin (CT) mediated ADP-ribosylation (ADP-R) of several proteins were determined by SDS-PAGE. The estrogen-treated pituitaries had an identical ADP-R Gs band (45 kDa) compared to the untreated ovariectomized controls. There was a marked alteration in labelled protein expression in the 25kDa range. No effects of estrogen treatment on CT catalyzed ADP-R in striatum or uterus were evident. Pertussis toxin-mediated ADP-R in the same tissue was not affected by estrogen treatment. The potential significance of the novel 25 kDa substrate for CT catalyzed ADP-R in AP with respect to signal transduction and mitogenesis remains to be clarified.

EXPRESSION OF CD44 IN MALIGNANT CELLS

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The expression of the p85 glycoprotein (CD44) in human brain and leukemic cells has been the focus of our laboratory for several years. The recent demonstration of the identity of Hermes, a molecule implicated in the adhesion of lymphocytes to endothelium, and of CD44 proteoglycan, raises interesting questions as to the role of this molecule on fibrous astrocytes in normal brain and in malignant cells of diverse origin. The expression of CD44-specific mRNA transcripts was analysed in several melanoma, leukemia and astrocytoma cell lines using a PBL32-cDNA clone (provided by E. Butcher, Stanford University, CA). The same three mRNA species of 5.0-, 2.3- and 1.7-kb were seen in all CD44-positive lines tested. Negative cell types included Nalm-6 leukemia line, Y79 retinoblastoma line and normal endothelial cells derived from umbilical cord vein. A correlation between the amount of surface antigen and the level of mRNA was observed. Blasts of immature pre-B ALL and myeloid phenotypes, obtained from patients with leukemia, expressed very high levels of CD44 as did the astrocytoma lines. CD44 molecules were purified from leukemic cells, treated with trypsin and CNBr and fractioned by HPLC. Three peptides could be aligned with the amino acid sequence deduced from the cDNA (residues 49-54, 59-66 and 309-323). The isolation of peptide 309-323 confirms the existence of a processed glycoprotein bearing the 72 amino acid long cytoplasmic tail. Two distinct forms of CD44 (Mr 85,000 and 77,000) can be seen in leukemic cells and may represent molecules cross-linked differentially to intracellular signal transduction and/or cytoskeletal elements. CD44 is expressed in large amounts on malignant cells and could play a role in the adhesion to matrix proteins and/or other cells within a tumor, in tumor invasiveness and in metastatic potential.

ORGANIZATION OF MOTOR NUCLEI SUPPLYING INTERVERTEBRAL MUSCLES OF THE CAT REVEALED BY MULTIPLE LABELLING

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In previous electromyographic studies we have shown that deep neck muscles have highly modulated patterns of recruitment during head movement. Spinalis dorsi, semispinalis cervicis and rectus capitis posterior (RC) are primarily active during elevation of the head whereas obliquus capitis caudalis (OCC) is strongly recruited during head turns. In this study we have used a multiple labelling method to examine the topographical organization of motoneurons supplying different intervertebral muscles. Intervertebral muscle nerves were isolated, cut, and exposed separately to one of three different retrograde tracers; fluorogold, fast blue and horseradish peroxidase. This method permitted us to compare directly the location of different motoneuron groupings in a single cat. Motoneurons supplying dorsal intervertebral muscles were arranged in overlapping cell columns from rostral C1 to mid C5. Cells serving the extensor RC interdigitated with those supplying the turning muscle OCC, suggesting that the topographical organization of the cell groupings may not be a major factor influencing the specialized recruitment of deep neck muscles.

LOW DOSES OF CENTRALLY ADMINISTERED SOMATOSTATIN INCREASES FOOD INTAKE IN RATS

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Somatostatin (SRIF) has a wide distribution in the brain and in the periphery suggesting that it plays a greater role than merely regulation of growth hormone release from the pituitary. One of these putative roles has been the regulation of feeding. Peripherally administered SRIF has been consistently reported to attenuate feeding. However the literature on the feeding effect of centrally administered SRIF is equivocal; most authors report an anorexic effect whereas others report no effect or even an increase in eating. Virtually all these studies have utilized doses in the nanomolar or higher dose range. We have previously reported that centrally injected growth hormone-releasing factor (GRF) in low picomolar range doses (0.2-40 pm) increases feeding, whereas nanomolar range doses decrease intake. To investigate whether SRIF has a similar low dose efficacy and to generally clarify SRIF's feeding effects, male Wistar rats were given intracerebroventricular (icv) injections of SRIF in doses ranging from 0.4 pm to 3 nm. The injections were carried out via surgically implanted guide cannulae aimed at the lateral ventricles. SRIF in doses 0.4, 1 and 40 pm significantly increased 1 hour but not 24 hour intake whereas 3 nm significantly decreased both 1 hour and 24 hour food intake. A feeding effective dose of SRIF (1 pm) had no effect on general locomotor activity as measured by photocell cages. Similarly, peripheral injections of 40 pm SRIF did not alter food intake. These results suggest that contrary to its peripheral anorexic effect, somatostatin in very low doses acts centrally, as does GRF, to facilitate food intake. Taken together with our previous work on GRF, this study further suggests that the somatotropin releasing system has central neurotransmitter-like feeding effects that might compliment its peripheral endocrine effects on growth hormone release.

ROLE OF OXIDATIVE DAMAGE TO THE AQUEOUS OUTFLOW SYSTEM IN THE PATHOGENESIS OF GLAUCOMA

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Glaucoma is a leading cause of blindness characterized by the elevation of intraocular pressure resulting in irreparable damage to the optic nerve. Hydrogen peroxide (H_2O_2) is a normal component of aqueous humor which undergoes detoxification by glutathione in the trabecular meshwork (TM). To investigate the hypothesis that oxidative damage to the TM can cause glaucoma, a series of perfusions were performed to determine the value of pig eyes as an experimental model of aqueous outflow and to determine the effects of H_2O_2 on facility at normal and glaucomatous pressures. Enucleated pig eyes were perfused with PBS + 5 mM glucose at various pressures to determine the relationship between pressure (P) and outflow resistance (R). The mean linear regression of the P-R lines for n=12 eyes was R=3.4±0.13P, in units of mmHg/ul/min, which is very similar to that observed in human eyes. Facility is normally observed to increase linearly with respect to time (i.e. "washout") when enucleated eyes are perfused in vitro for all species studied except for humans. Expressed in units of ul/min/mmHg/hr, washout in pig eyes was found to be 0.0038 at 7.5 mmHg and 0.0147 at 30 mmHg, varying roughly in proportion to pressure. The effects of H_2O_2 on washout were studied by paired perfusions of enucleated pig eyes with PBS + 5 mM glucose in the control eye and the same solution with the addition of 3 mM H_2O_2 + catalase inhibitor + glutathione inhibitor (1 mM BCNU) in the experimental eye. At a pressure of 7.5 mmHg, washout increased in the experimental eye relative to the control by 0.012±0.013 (n=13, p=0.01), but at an elevated pressure of 30 mmHg, washout in the experimental eye decreased relative to the control by -0.033±0.043 (n=13, p=0.02). This result suggests that the effect of oxidative damage on outflow is pressure-dependent and that elevated pressure associated with glaucoma may increase the susceptibility of such eyes.

OSTEODIFFERENTIATION AND TRANSFORMATION SUSCEPTIBILITY

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Most cancers may be depicted by heterogeneous subpopulations of poorly differentiated and rapidly proliferating cells. Evidence has also accumulated describing how such cells, in contrast to their elimination by cytotoxic agents, may be "rehabilitated" in certain tissues, to a more functionally mature phenotype under the influence of differentiation agents. Accordingly, it was hypothesized that induced differentiation of osteoblasts in chicken embryo periostea (CEP) would render these cells less susceptible than osteoprogenitor cells, to transformation by the $P140^{gag\text{-}fps}$ oncoprotein of Fujinami avian sarcoma virus (FSV). In order to determine whether osteoprogenitor cells were more susceptible to transformation than their differentiated progeny, the following procedures were carried out. CEP cultures were infected at various periods of incubation, during which time osteoprogenitor cells developed into mature osteoblasts. Thus if FSV infection occurred early in culture, osteoprogenitor cells became infected, whereas at later stages, FSV exposure resulted mainly in the infection of mature osteoblasts. In another experiment, CEP cultures were exposed to dexamethasone (an agent which induces osteoblast differentiation) prior to infection. In either case, when CEP cultures containing mainly differentiated osteoblasts were infected with FSV, transformation did not occur. Alternatively, when CEP cultures containing primarily osteoprogenitor cells were infected with FSV, osteosarcomatous transformation occurred readily. In fact, cultures from the latter group, and not the former, exhibited the ability to produce tumours in athymic mice. Taken together, the aforementioned findings suggest that undifferentiated CEP osteoprogenitor cells are more susceptible to oncogene-mediated (FSV) transformation than their more differentiated progeny.

A MOLECULAR ASSAY FOR VDJ RECOMBINASE ACTIVITY IN MURINE PRE-B CELL LINES

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During B-cell differentiation, functional immunoglobulin (Ig) genes are assembled from a large number of distinct gene segments. The Ig gene heavy chain variable region is derived from the joining of V_H (variable) and D_H (diversity) and J_H (joining) gene segments. It is believed that VDJ recombination is carried out by a recombinase enzyme. The objective of this study was to demonstrate a relationship between the level of recombinase activity and the developmental stage of recombination in Abelson murine leukemia virus-transformed pre-B cell lines. A plasmid vector, pJH201, has been described (Hesse, J. et al., Cell 49:775-783, 1987) which permits the evaluation of the recombinase activity in a cell line. The plasmid contains a prokaryotic stop sandwiched between Ig recombination signal sequences; the stop signal blocks the expression of a downstream chloramphenicol (Cam) resistance gene. After transfection into cells with VDJ recombinase activity, the stop signal is excised and the plasmid is able to confer Cam resistance when transformed into *E. coli*. The frequency of Cam-resistant colonies so obtained provides a relative measure of the recombinase activity of the cell line. The optimal conditions for performing the assay were determined and our results suggest that higher levels of recombinase activity were found in DJ/DJ cell lines as compared to VDJ/VDJ cell lines. Recombinase activity can be detected in VDJ/VDJ cell lines, suggesting that full rearrangement at the IgH locus does not limit the expression of the recombinase enzyme.

THE ROLE OF BASIC FIBROBLAST GROWTH FACTOR IN REVASCULARIZATION OF RABBIT TRACHEAL AUTOGRAFTS

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Donor airway ischemia and inadequate anastomotic healing continue to be significant problems following lung transplantation. Angiogenic properties have been ascribed to a variety of protein and lipid extracts. The influences of surface abrasion and topical application of basic Fibroblasts Growth Factor (bFGF) on omental revascularization of rabbit tracheal heterotopic autografts were studied. Eight ring segments of cervical trachea were excised, primary tracheal anastomoses performed, and the tracheal segments placed in the peritoneal cavity securely wrapped in omentum. Animals were randomly allocated to one of six groups according to treatment given to the tracheal segments: control, surgical abrasion, Surgicel wrap combined with topical bFGF application, Surgicel wrap combined with topical bFGF diluent application, Gelfoam wrap combined with topical bFGF application, and topical bFGF application alone. Prior to sacrifice one week later, animals were heparinized and perfused with Aquablak dye. Tracheal segments were excised and sectioned for light microscopic quantitative assessment of viability and extent of dye perfusion. There was no significant improvement in viability or perfusion between abraded and bFGF treated tracheal segments when compared to control segments. Airways wrapped in Surgicel had a significantly greater degree of ischemic injury compared to the control group, regardless of bFGF application. Neither surgical abrasion nor application of bFGF increased omental revascularization of transplanted tracheal segments after seven days.

NUCLEAR PROTEINS INTERACTING WITH THE 5' FLANKING REGION OF THE HUMAN GENE FOR GRANULOCYTE/MACROPHAGE COLONY-STIMULATING FACTOR

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The leukemic blasts of some patients with AML have been shown to require GM-CSF for growth, express GM-CSF message and secrete GM-CSF protein, suggesting that GM-CSF plays an important role in the growth of AML in vivo. In order to begin to elucidate the transcriptional regulation of the gene for GM-CSF in AML and other cell types, we have used the gel mobility shift assay to determine portions of the GM-CSF gene that bind nuclear proteins. Nuclear proteins were prepared from an AML cell line in addition to 5637, a bladder carcinoma cell line; both cell lines express GM-CSF RNA as determined by nuclear run-on experiments. We found that two Fok I fragments, -585 to -343 (fragment B) and -343 to 43 (fragment A), bind protein in a specific manner. Furthermore, the binding of fragment A could compete out the specific binding of fragment B and fragment B could compete out the specific binding of fragment A. Both fragments contain a lymphokine consensus sequence. We constructed an oligonucleotide that spanned the lymphokine consensus sequence and found that it could not bind nuclear protein nor compete out the protein binding to fragment A or B. We found smaller subfragments of fragments A and B that could however bind nuclear protein.

CHOLECYSTOKININ ANTAGONIZES THE ACTION OF DOPAMINE IN THE VENTRAL STRIATUM: POSSIBILITY OF AN IMPROVED TREATMENT FOR SCHIZOPHRENIA

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The striatum is innervated by dopamine (DA) containing neurons originating in the midbrain substantia nigra and ventral tegmental area (VTA). DA neurons that project to the dorsal striatum (caudate nucleus) have been implicated in the pathogenesis of Parkinson's disease whereas those that project to the ventral striatum (nucleus accumbens) have been implicated in the development of schizophrenic psychosis. Because of its clinical significance, a great deal of research has been devoted to the understanding of the cellular actions of DA in these brain areas. It has previously been shown that DA has a neuromodulatory action in the nucleus accumbens (NAcc). It attenuates the synaptic response of NAcc neurons to afferent inputs from the amygdala (AMY) without producing a direct synaptic action of its own. We report here that cholecystokinin (CCK-8), which has recently been demonstrated to co-exist and appears to be co-released with DA in the NAcc, specifically antagonizes the neuromodulatory action of dopamine in the NAcc. In a series of electrophysiological experiments, single neuron recordings were made in the NAcc of urethan anaesthetized male Wistar rats. These neurons were strongly excited by electrical stimulation of AMY and concurrent stimulation of VTA attenuated the responses, presumably due to DA release. Microiontophoretic application of proglumide (PRG), a CCK-8 antagonist, enhanced the attenuating effect of VTA stimulation by 32-126%. Iontophoretic application of DA or GABA produced similar attenuation of responses to AMY stimulation. The attenuation by DA (but not that by GABA) was in turn reversed by concurrent iontophoresis of CCK-8. CCK-8 by itself did not produce significant effect on the spontaneous activity of the neuron nor its response to AMY stimulation. These results are the first electrophysiological evidence that exogenous and endogenous CCK-8 may modify the postsynaptic action of DA in the NAcc in addition to modulating its release as shown in other studies. The finding has a significant implication in the treatment of schizophrenic psychosis. A CCK-8 analogue used in conjunction with conventional neuroleptics may offer better control of the mental disorder without Parkinsonian side effects.

ACUTE PULMONARY EFFECTS OF AEROSOLIZED PENTAMIDINE - A RANDOMIZED CONTROLLED STUDY

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From June 1988 to February 1989, we enrolled 36 HIV-positive patients into a randomized double-blind placebo-controlled trial to assess the acute pulmonary toxicity of aerosolized pentamidine (AP) as secondary prophylaxis for *Pneumocystis carinii pneumonia*. Each patient underwent spirometric studies pre- and post-aerosolized treatment. There was no significant difference in the baseline pulmonary function tests (PFT) between the two groups. Eleven (65%) patients in the AP group developed cough but only four demonstrated a modest but significant reduction in the flow rates post-AP (pre FEV_1/FVC - 80%, and post FEV_1/FVC - 72%), four (21%) patients in the placebo group developed cough, but no significant change in the flow rates was noted (pre FEV_1/FVC - 85%, and post FEV_1/FVC - 86%). All bronchospastic episodes were self-limited and responded to remedial inhaled salbutamol treatment. We conclude that AP treatment is frequently associated with coughing attacks (65%) but the actual incidence of bronchospasm on PFT is much lower (24%) and is generally quite mild.

AWARD WINNERS

A competition is held as part of Research Day to recognize the most outstanding presentations. This year's excellent judges were Drs. Bayliss, Csima, Murray, Salerno, Whiteside and Wiley. We would like to acknowledge and thank those who participated in and helped to organize Research Day and make it the success that it was. Additional thanks are in order to Dr. David Jenkins for his entertaining address at the Research Day banquet held the same evening.

The following students won the George Brown Memorial Award, including a prize of $166:

Alan Barolet 9T2
Martin Breton 9T3
Dae-Gyun Chung 9T2
Janice Johnston 9T3
Amin Kassam 9T1
Patrick Lo 9T0
Allison McGee 9T2
Marion Perpick-Dumont 9T3
Andrew Smith 9T0
Barry Sullivan 9T1
Elizabeth Tham 9T2
David Yan 9T2
Conrad Yim 9T3
Scott Young 9T3
Joint Prize: Karen Cheung 9T2, Rakesh Jetly 9T1, Jane Kim 9T1, Brian Ling 9T1, Alden Pearl 9T1, David Satok 9T1, Dorothy Sit 9T2.

Martin Breton 9T3, Patrick Lo 9T0 and Barry Sullivan 9T1 received the ultimate honour of representing the University of Toronto Medical School at the 31st Annual National Student Research Forum in Galveston, Texas, April, 1990. Congratulations to all participants in Research Day for your outstanding work and accomplishment.